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Interstitial pulsed-dose-rate brachytherapy for head and neck cancer—Single-institution long-term results of 385 patients

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ABSTRACT

PURPOSE: To assess the long-term results of protocol-based pulsed-dose-rate (PDR) interstitial brachytherapy (iBT) in 385 patients with head and neck cancer who underwent PDR-iBT preferably after minimal, nonmutilating surgery.

METHODS AND MATERIALS: From 1997 to 2009, a total of 385 patients received protocol-based PDR-iBT for head and neck cancer. Brachytherapy was preceded by surgery in most of our patients (326/385, 84.7%). Altogether, 246 of 385 patients (63.9%) received iBT alone and 135 of 385 patients (36.1%) in combination with external beam radiation therapy. The analysis was done after a median followup of 63 months.

RESULTS: The 5-, 10-, and 15-year local relapse-free survival rates according to Kaplan–Meier test for all analyzed patients were 85.8%, 83.1%, and 80.2%, respectively. The 5-, 10-, and 15-year overall survival and disease-free survival rates were 68.9%, 52.2%, and 44.1%, and 81.3%, 79.3%, and 76.3%, respectively. For N0-/N1- vs. N2-patients, we observed significantly different 5-year local recurrence-free survival rates with values of 92.3% and 73.7%, respectively ($p = 0.007$). No other patient or treatment-related parameters had a significant influence on treatment results. Serious late side effects, such as soft tissue or bone necrosis, were observed in 39 of 385 patients (10.2%) and 18 of 385 patients (4.9%), respectively.

CONCLUSIONS: The PDR-iBT with 0.4–0.7 Gy each hour, 24 h per day for patients with head and neck cancer is a proven, effective, and safe treatment method with excellent long-term data.

Keywords: Pulsed-dose-rate brachytherapy; Interstitial brachytherapy; Head and neck

Introduction

Interstitial brachytherapy (iBT) as a sole treatment or in combination with external beam radiation therapy (EBRT) is a valuable treatment modality in the treatment of both primary and recurrent head and neck cancer. The results of low-dose-rate (LDR) brachytherapy with ^{192}Ir wires using the rules of the Paris system were considered gold standard in the therapy of preferably small head and neck tumors up to the end of 20th century (1–14). Pulsed-dose-rate (PDR) brachytherapy as a substitute for LDR brachytherapy is considered a useful option in the treatment of head and neck tumors because it combines the biologic advantages of LDR brachytherapy (15–18) with the technical advantages of the afterloading technique known from high-dose-rate (HDR) brachytherapy.

This article presents a single-institution experience of protocol-based PDR-iBT for 385 patients with special emphasis on local control rate and late toxicity in patients with squamous cell carcinoma of the oral cavity and of the oropharynx who underwent PDR-iBT preferably after minimal, nonmutilating surgery.

Patients and methods

From October 1997 to December 2009, 385 patients received protocol-based PDR-iBT for head and neck cancer. Patient and tumor characteristics especially with regard to tumor site and stage (Table 1) illustrate that most patients had tumors of the oral cavity (72%). Mainly, the

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Table 1
Tumor characteristics

Characteristics	Number of patients ($N = 385$), n (%)
Tumor site	
Lip	14 (3.6)
Floor of mouth	118 (30.6)
Base of tongue	33 (8.6)
Mobile tongue	160 (41.6)
Soft palate	12 (3.1)
Tonsil	34 (8.8)
Buccal mucosa	11 (2.9)
Nasopharynx	2 (0.5)
Hard palate	1 (0.3)
Tumor stage	
T1	172 (46.2)
T2	167 (44.9)
T3	17 (4.6)
T4	14 (3.8)
Tx	15 (4.0)
Nodal stage	
N0	253 (65.7)
N1	56 (14.5)
N2	57 (14.8)
Nx	6 (1.6)
Histology	
Squamous cell carcinoma	359 (96.5)
Adenoid cystic carcinoma	5 (1.3)
Others	8 (2.2)
Grading	
G1	38 (10.2)
G2	221 (59.6)
G3	101 (27.2)
G4	2 (0.5)
Not classified	2 (0.5)
Not known	21 (5.4)
Lymphovascular invasion	
Negative	197 (53.1)
Positive	87 (23.5)
Not known	101 (27.1)

tumors (70%) were well or moderately differentiated squamous cell carcinomas with 91% being in Stage T1/T2.

In most of our patients (326/385, 84.7%), brachytherapy was preceded by surgery. The surgical procedures for all these patients included tumor resection with neck dissection. The time interval between surgery and radiation therapy was 63 days (median). The indication for postoperative brachytherapy predominantly was positive or close resection margins (≤2 mm), or in the case of clear resection margins if there were risk factors such as a depth of tumor invasion of more than 5 mm, lymphovascular invasion, or histopathologic grading of 3 or 4. Clear resection margins had been achieved in 300 of 326 (92%) patients. The median value for depth of tumor invasion was 7.0 mm. A total of 139 of 385 patients (37.4%) with large tumors or positive lymph nodes were treated in addition with EBRT with a median dose of 55 Gy. The median for the time interval between EBRT and brachytherapy was 9 days. All patients were treated with PDR-iBT with ^{192}Ir. All implants were done under general anesthesia using plastic tubes and respecting the rules of International Commission on Radiation Units and Measurements 58 (19) as described by us in detail earlier (20, 21). A dose per pulse (dp) with a median value of 0.55 Gy (range, 0.4–0.7 Gy) was used, delivered for 24 h per day with a time interval of 1 h between pulses. The median volume of the 85% isodose (reference isodose) was 23.4 cm^3. The median values for the dose homogeneity index and the dose nonuniformity ratio were 0.76 and 0.27, respectively. For 113 of the 385 (29%) patients treated since 2007, a delineation of the clinical target volume (CTV) and the organs at risk using CT-based treatment planning has also been performed. The CTV encompassed the macroscopic tumor/tumor bed (gross tumor volume) and a 5–10-mm safety margin in all directions respective of natural, anatomic borders such as bone, the lingual edge, and the skin. In postoperative cases, the tumor bed contour (gross tumor volume) included all clinically visible and palpable surgical scars. For CT-based planning, the dose distribution was normalized on reference points in the central plane according to International Commission on Radiation Units and Measurements 58. Thereafter, a geometric optimization was done to achieve the best possible dose homogeneity. In a last step, the dwell times were adjusted manually or using graphical optimization aiming to achieve a satisfactory coverage of the CTV. Here also, the coverage index V_{100} (median, 93.3%) and D_{90} (median, 103.8%) were documented.

A total of 246 of the 385 patients (63.9%) received iBT procedures alone using a median total dose of 57 Gy. In combination with EBRT, PDR-iBT was performed with a median total dose of 24 Gy. The median time interval between external irradiation and brachytherapy was 9 days. The EBRT was performed up to a median reference dose of 55 Gy.

Patients with T4 tumors or positive lymph nodes with extracapsular tumor extension (47/385, 12.6%) additionally received simultaneous chemotherapy in the first and fifth weeks of EBRT using Cis-/Carboplatin and 5-fluorouracil.

The statistical analysis was performed with the SPSS 18.0 software (IBM Corp., New York). The actuarial curves were calculated according to the Kaplan–Meier method (22). The comparisons were made using the log-rank test or Cox regression analysis or the Kruskal–Wallis test as appropriate. All patients were followed closely to analyze local control, survival, as well as acute and late toxicity. The analysis was performed after a median followup of 63 months. The followup was calculated from the first day of radiation therapy to the date of last followup.

Results

The 5-, 10-, and 15-year local relapse-free survival rates according to Kaplan–Meier test for all analyzed patients were 85.8%, 83.1%, and 80.2%, respectively (Fig. 1). The 5-, 10-, and 15-year overall survival and disease-free

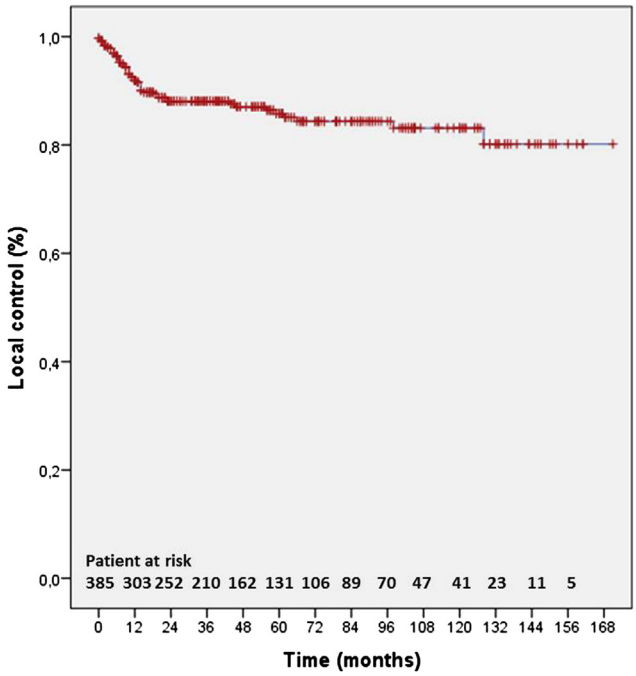

Fig. 1. Local control rate according to Kaplan–Meier analysis for all patients.

survival rates were 68.9%, 52.2%, and 44.1%, and 81.3%, 79.3%, and 76.3%, respectively. There were a total of 48 local recurrences (LRs) among the 385 patients: 16 LR for the 172 T1 patients, 25 LR for the 167 T2 patients, 5 LR for the 17 T3 patients, and 2 LR for the 14 T4 patients. Nearly, all LRs (40/48) developed in the first 3 years after therapy, the mean time to LR was 20 ± 26 months (Fig. 2).

The 5-and 10-year LR-free survival rates of the entire group according to tumor size and nodal status were 91.3% and 90.5 for stage T1/2 N0/1 and 80% for stage T1/2 N2, respectively (Fig. 3). For the small number of patients with large tumors such as T3/4 N0/1 or T3/4N2 (31/385), the 5-year LR-free and overall survival rates were 88.9% and 51.1%, respectively.

In the detailed analysis of all patients, we did not identify any statistically significant differences with respect to anatomic site or tumor size. We found a significant influence of the extent of lymph node involvement on treatment results. In N0-/N1- vs. N2-patients, we observed significantly different 5-year LR-free survival rates with values of 92.3% and 73.7%, respectively ($p = 0.007$, Fig. 4). No other tumor- or patient-related factor showed a significant correlation with treatment results either in univariate or multivariate analysis. Regarding treatment factors, we only identified surgery to have a significant influence on treatment results. The 5-year LR-free survival was 93.4% with surgery and 72% without surgery ($p = 0.002$). In this context, it is important to note that there was a considerable negative selection bias affecting prognosis in patients without surgery—for patients with or without surgery, large tumors (T3/T4) were recorded in 6.5% and 25%, respectively and N2 status in 12.1% and 37.5%, respectively.

During followup, we observed metastases in 41 of 385 patients (10.6%). Only 13 of 385 (3.4%) patients developed regional lymph node metastases, the other 28 of 385 (6.2%) patients developed distant metastases. The median time to appearance of metastases was 12 months.

Serious late side effects, such as soft tissue or bone necrosis, were observed in 39 of 385 patients (10.2%) and 18 of 385 patients (4.9%), respectively. In patients with

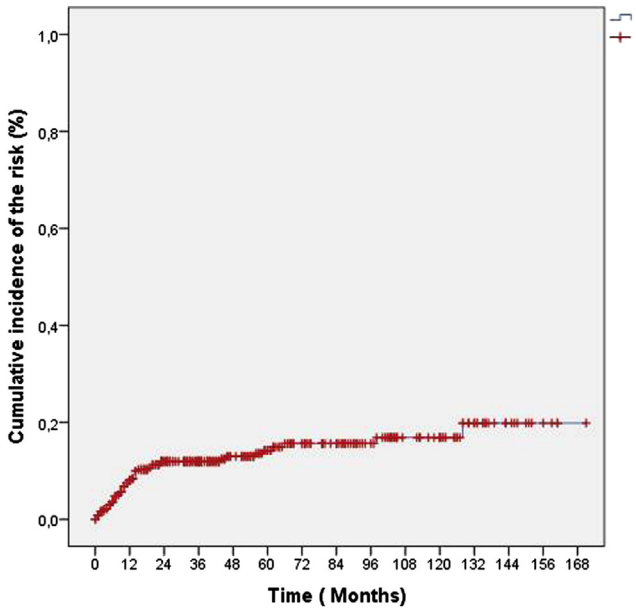

Fig. 2. Cumulative incidence of the risk of local recurrence for all patients.

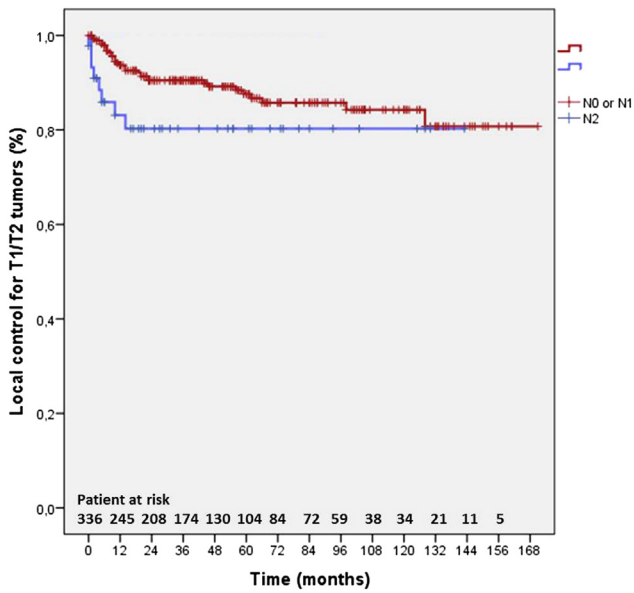

Fig. 3. Local control rate according to Kaplan–Meier analysis for patients with small tumors (T1/T2) according to lymph node status.

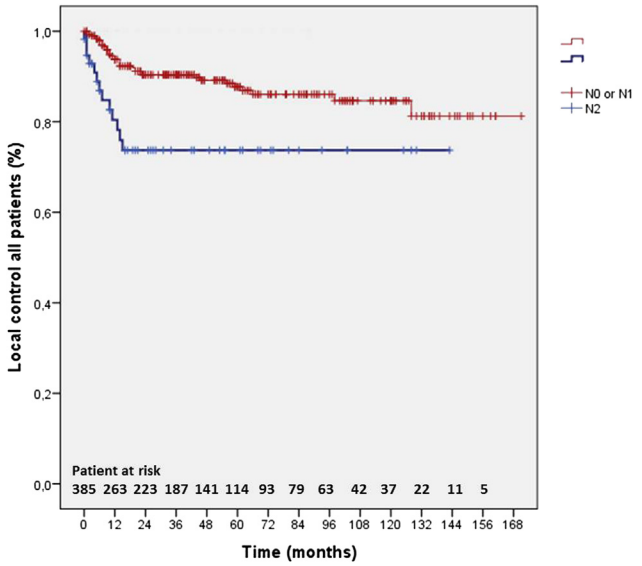

Fig. 4. Local control rate according to Kaplan–Meier analysis for all patients according to lymph node status.

soft tissue necrosis, further surgical treatment was necessary in 13 of 39 (13/385, 3.4%) patients; in patients with bone necrosis, surgical treatment was necessary in 13 of 18 (13/385, 3.4%) patients.

Discussion

For tumors of the oral tongue treated with primary LDR brachytherapy, we know from large retrospective series that the local control rate strongly depends on tumor size and varies between 62–69% for T3 tumors and 88–93% for T1 tumors (2–8, 10, 21, 23–27). Treatment success is strongly related to the total dose and the dose rate as shown in the results presented by Mazeron *et al.* (2, 26) and Simon *et al.* (9)—these should be higher than 62.5 Gy and higher than 0.5 Gy/h, respectively. The published local control rates for oral cavity cancer vary between 75% and 90% and are strongly related to tumor size, total dose, and dose rate. For oropharyngeal carcinomas without surgery treated with LDR brachytherapy combined with EBRT, the largest series were reported by Senan and Levendag (28). The 5-year local control rates in 243 patients were between 67% (T3 tumors) and 87% (T1/T2 tumors). Similar results were reported from other centers (14, 29–31). Some of the best results for brachytherapy as boost for early oropharyngeal cancer without surgery has been reported recently by Al-Mamgani *et al.* (32)—for 167 patients, a 5-year local control rate of 94% was achieved. In the postoperative setting, brachytherapy as boost (pT1/T2 pN+ patients) and in particular postoperative brachytherapy alone (pT1/T2 pN0 patients) offers the patients the same 5-year local control rates as EBRT—about 90% (4, 11, 21, 26, 33–36)—with much lower side effects. Brachytherapy avoids xerostomia, extensive mucositis affecting the whole oral cavity, trismus, and also permits future radiation therapy of possible secondary tumors in the head and neck area owing to the excellent protection of surrounding healthy tissues.

Radiobiologic studies have shown that PDR brachytherapy is probably equivalent to LDR brachytherapy models (15–18, 37–44). Clinical data derived from different clinical situations has provided some evidence to support this hypothesis (20, 21, 45–55). Unfortunately up to now, for head and neck cancer treated with PDR brachytherapy, only a limited amount of experience has been presented in the literature—mostly in the form of feasibility studies with limited patient numbers (26, 47–49, 51, 56, 57). The French experiences with PDR brachytherapy for 30 head and neck cancer patients (51) have only been able to show that PDR brachytherapy is feasible and that 14 of 28 patients had short or definitive breakdown of therapy owing to different problems. Similarly, de Pree *et al.* (49) have shown in 17 patients that PDR brachytherapy is feasible. Levendag *et al.* (56) have treated 38 patients with head and neck cancer with PDR brachytherapy (dp = 2 Gy, 4–8 times/d) alone or in combination with EBRT. The patients showed better local control as compared with a historical control group (87% vs. 61%).

Some centers have also introduced daytime PDR schedules to avoid hospitalization and to reduce overall treatment costs. Whether it is possible to restrict PDR irradiation only to office hours without compromising therapy efficacy (53, 58) remains controversial. Until now, no long-term results of any study support this suggestion. We believe that only the complete 24-h treatment schedule guarantees that PDR brachytherapy will preserve all the radiobiologic advantages of LDR brachytherapy. In our experience, there exist no logistical or practical problems with the 24-h treatment schedule of PDR brachytherapy administered for 3–6 days.

If we compare our results from PDR-iBT in head and neck cancer, mostly administered as postoperative brachytherapy, with the results from LDR brachytherapy (14, 33–35, 59, 60), we see prevailing similarities in the results. The reported local control rates depend on the tumor size have values between 78% and 93% for T1/T2 tumors and 57% for T3/T4 tumors (3, 6, 14, 21, 27, 33, 34, 59, 60). Local control rates in our study also correlate with tumor size and reach 86% after 5 years and 83% after 10 years for all patients. In this context, it is necessary to mention the limitations of the Kaplan–Meier method for local control estimates because competing events such as deaths from other causes can modify the results. Nonetheless, it is obvious that such excellent local control rates have been achievable only in the era of modern image-guided brachytherapy, with optimal interleaving of brachytherapy and nonmutilating surgery. In this context, our results are also congruent with excellent results of Al-Mamgani *et al.* (32). Recently, there has also been a sharp increase in the

use of HDR brachytherapy for the treatment of head and neck tumors. Data relating to HDR brachytherapy in the treatment of head and neck cancer have been largely retrospective (21, 56, 61–70), but there exists one randomized study (65) with a relatively small number of patients. Unfortunately, in the randomized study, only 59 patients were analyzed and therefore no valid conclusions can be drawn. The retrospective results seem to indicate that the results of HDR brachytherapy may be similar to the results of LDR and PDR brachytherapy.

The most feared serious side effects are soft tissue and bone necrosis. The probability for this complication depends in particular on the total dose, dose rate, intersource spacing, implant volume, quality index, and volume gradient ratio (9, 27, 71–73). Osteoradionecrosis also correlate with the distance between the sources and the bone. The risk of soft tissue necrosis in LDR brachytherapy varies between 20% and 30%—most of these lesions heal spontaneously and necrosis of bone may occur in about 10–20% of the patients. For example, Lapeyre *et al.* (35) reported late complications in 34 of 82 patients (43%), 8 of them (9.8%) were in Grade 3. Beitler *et al.* (33) reported a high rate of late side effects—with severe or moderate late sequelae being seen in 12 of 23 patients (52.2%). Similarly, in a series reported by Mendenhall *et al.* (36), 7 of 15 patients (46.7%) developed serious late complication. In our study, we registered serious late side effects in 5–10% of the patients with only 3.4% suffering from soft tissue or bone necrosis requiring surgery. We suggest that these low complication rates are first owing to the exclusive use of PDR brachytherapy in all patients, a therapy method, which unites the biologic advantages of LDR brachytherapy with the technical advantages—the stepping source technology—of the HDR-afterloading method and second owing to consequent consideration of quality assurance (72).

The results of our protocol-based study in 385 patients—up to date the largest series worldwide—demonstrate that PDR brachytherapy is really biologically equivalent to LDR brachytherapy. The presented results confirm the radiobiologic hypothesis that PDR brachytherapy is indistinguishable from continuous LDR brachytherapy, if the pulses are given for more than 3–7 days once per hour, 24 h per day with dps of between 0.4 and 0.7 Gy.

Moreover, it seems that owing to the possibility of optimization of the source times, the results of PDR brachytherapy may be superior to the results of LDR brachytherapy in terms of its potential for individualization and the possibility of a better treatment schedule—in particular regarding late side effects.

Conclusions

The PDR-iBT with dps of 0.4–0.7 Gy each hour, 24 h per day for the treatment of head and neck cancer in selected patients is a proven, effective, and safe treatment method with excellent long-term data.

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